Remarks

Claims 28-30 and 42-49 are pending in the application. Claims 42-49 are new.

All claim cancellations and amendments are made without prejudice to the filing of one or more continuing applications.

Claim 28 has been rewritten in independent form. Support for the amendment is found in claim 1, which has been cancelled.

New claim 42 is based on previous claim 2 and claims 43 to 49 are based on previous claims 18 to 27. Further support for the new claims is found in the specification as follows:

claim 42: p. 3, lines 24-29;

claim 43: p. 6, line 29, to p. 7, line 2;

claim 44: p. 7, lines 4-10;

claim 45: p. 7, lines 12-17;

claim 46: p. 7, lines 12-17;

claim 47: p. 7, lines 12-17;

claim 48: p. 7, lines 19-22; and

claim 49: p. 7, lines 24-29.

A Statement of Biological Deposit is submitted herewith in support of the deposit of ECACC 0312041 ECACC 03112701, as recited in the specification at page 5, lines 9-12, and page 7, lines 24-29.

Response to 35 U.S.C 103 Rejection

The Examiner alleges that claims 28-30 are unpatentable over Martens et al, in view of Barksi et al, because the Examiner considers that at the time of the invention, it would have been obvious to utilize the ecdysone-inducible expression system of Barski et al in the method of Martens et al. Examiner alleges that Barski et al teaches that vectors encoding a p35 and p40 subunit of IL-12 were available and successfully used. Further, the Examiner alleges that in relation to claim 28, step (i), "Martens et al teaches a method comprising incubating a cell culture comprising cells transfected with a

baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, under the control of an inducible promoter with a compound of interest to test the ability of the compound to inhibit dimer assembly".

Applicant disagrees with the Examiner's interpretation of Martens et al. Martens et al. is a paper from the inventors' own group. Applicant respectfully submits that the objectives and subsequent conclusions of the Martens et al. paper are incorrectly characterized by Examiner.

Martens et al. is concerned with two expression systems, a baculovirus expression system which is not inducible and an inducible bacterial expression system. It discusses the utilisation of these two different expression systems in two different studies.

As described at page 6681 of Martens et al, the baculovirus expression system is used as a "test system". As this baculovirus expression system was known to successfully express porcine p40, Martens et al. utilised the baculovirus expression system to confirm that the addition of a histidine tag to p40 did not prevent expression or dimerization of porcine p40 (see page 6680 column 1). The baculovirus expression system was not inducible and was only used to assess proper, natural, dimerization of secreted p40.

Thus, in contrast to the Examiner's assertion, Martens et al does not "teach a method comprising incubating a cell culture comprising cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, *under the control of an inducible promoter* with a compound of interest to test the ability of the compound to inhibit dimer assembly".

The bacterial expression vector, inducible with the chemical compound IPTG, discussed by Martens et al, was used to express p40 in a monomeric form which was deposited as an aggregated form in insoluble inclusion bodies (see for example page 6679, first two paragraphs of right hand column). The study by Martens et al utilised the insoluble monomeric p40 expressed by the bacteria to determine a procedure to purify and solubilize the insoluble monomeric p40 from the inclusion bodies. Additional

experiments were then undertaken to promote the formation of dimmers from the monomeric p40 *in vitro* using foldases and chaperones (see page 6680, left column, starting at line 31 of Martens et al.).

The aim of the study using the bacterial expression system was to determine conditions to enhance dimer assembly starting from recombinant *E. coli* (bacterial)-produced porcine p40. This contrasts the method of "inhibiting dimer assembly" as described and claimed in the present application. The teaching of Martens et al in relation to "enhancing dimer assembly" completely contrasts the aim of the present application and is completely different in terms of experimental set up, goals/objectives and biological source material used. Even although both focus on IL-12 subunits, the skilled person would not consider Martens et al. to teach or suggest a method of inducing p40 expression to test the ability of a compound to inhibit dimer assembly.

Moreover, "Inhibition" of interleukin dimer assembly according to the present invention is obtained via compounds that act upon the producer cell by changing the secretory pathway of IL-12 subunits, such that these subunits do not dimerize and are not secreted. This is clearly set out in amended claim 28.

In distinct contrast, "enhancement" as described in Martens et al., is based on *in vitro* experiments in which monomeric unfolded/misfolded IL-12 is provided in dimeric form using buffer compounds and foldases, not using cell-based assays as in the present invention.

Therefore, in contrast to the Examiner's assertion, Martens et al does not teach a method comprising incubating a cell culture comprising cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, under the control of an inducible promoter with a compound of interest to test the ability of the compound to inhibit dimer assembly.

Accordingly, the present methods cannot be considered as a variation of the approach characterized by Examiner as "testing of compounds that affect the dimerization of subunits of IL-12 using expression vector systems". One cannot predict

the method or approach needed to *inhibit* IL-12, when starting from the methods used to *enhance* IL-12 dimers as described and taught in Martens et al.

With respect to the Examiner's statements regarding the relevance of Barski et al. (office action, bottom of page 4 and in page 5), Applicants submit these comments are only partially correct. There is no evidence to support the Examiner's statement that "Barski et al teach that their vectors encoding a p35 and the p40 subunit were available and were successfully used". In Barski, the recombinant DNA vector, based on the aldehyde reductase gene, (see claim 9 of the Barski patent document) is available, but all the DNA sequences provided in the Barski patent appear to constitute fragments that function as bidirectional promoters. The vector described in the Barski patent contains a bidirectional promoter to regulate expression of two separate genes. Further, Barski provides examples of where co-expression of two genes could be conceived to form functional heterodimers. However, the prior art document does not provide evidence of DNA sequences coding for p40 or p35, nor does it provide evidence that vectors encoding p35 and p40 were either available or successfully used. All DNA sequences provided in the Barski patent (SEQ ID NO.19....NO.31, page 61) represent fragments of the aldehyde reductase promoter in which no identification of p40 or p35 in these DNA sequences can be made.

In the last paragraph of page 5 of the office action, Examiner outlines the reasons why it would have been allegedly obvious at the time of the invention to utilize the ecdysone-inducible expression system of Barski et al in the method of Martens et al. As already outlined above, the purpose of Martens et al. is to reconstitute dimeric (p40) starting from solubilized bacterial inclusion bodies, not to test compounds inhibiting dimerization of IL-12 subunits.

There would have been no point in using the ecdysone inducible expression system of Barski in the work performed by Martens et al, as the aim of Martens was to study the parameters that affect refolding of p40, starting from p40 purified from inclusion bodies. The Martens et al paper was precisely and specifically intended to define conditions supporting formation of dimeric p40 forms *in vitro* by means of

enzymatic (foldase-based) methods starting from monomeric p40. In addition, there appears to be no evidence in the Barski patent to contemplate testing compounds that affect dimerization of subunits of IL-12 using expression vector systems.

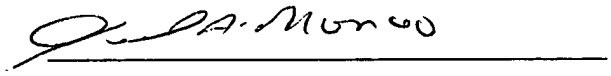
In conclusion, it is respectfully submitted that Examiner has misinterpreted the teaching of both Martens et al., and Barski et al. Based on these incorrect interpretations, and with knowledge of the present invention, the Examiner has incorrectly combined the cited teachings to reach the incorrect conclusion that the invention of claim 28 would have been obvious.

For the reasons stated above, the invention of claim 28 would not have been obvious to one of ordinary skill in the art in view of the asserted references. Claim 28 is therefore patentable. Claims 29, 30 and 42-49, which depend from claim 28 and recite additional features of the claimed method, are likewise allowable.

The claims remaining in the application are in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

KOEN VANDENBROECK, et al.



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